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Clinical Trial Simulation of a 200- μ g Fixed Dose of Darbepoetin Alfa in Chemotherapy-Induced Anemia

ABSTRACT

Our objective was to assess, using clinical trial simulation, the feasibility of a fixed 200- μ g dose of darbepoetin alfa (Aranesp) administered every 2 weeks in chemotherapy-induced anemia. A pharmacokinetic/pharmacodynamic model was developed using clinical data from 547 cancer patients who received darbepoetin alfa at various doses and schedules. Monte Carlo simulations were performed for weight-based (3 μ g/kg every 2 weeks) and fixed-dose (200 μ g every 2 weeks) regimens and were compared with observed clinical data. Mean hemoglobin changes from baseline to end of treatment were +1.61 g/dL, +1.83 g/dL, and +1.79 g/dL for observed data, the weight-based simulation, and the fixed-dose simulation, respectively. The rates of required transfusions (hemoglobin \leq 8 g/dL) were also similar between groups. For patients between 45 and 95 kg (over 90% of the population), the impact of a fixed dose on mean hemoglobin change was negligible. There was a slight weight effect at body weight extremes (< 45 kg and > 95 kg). Clinical outcomes from simulations of weight-based and fixed dosing of darbepoetin alfa were similar to those of observed weight-based data. Given the weight distribution of a typical cancer population, the majority would be expected to benefit equally from weight-based and fixed-dose darbepoetin alfa in the amelioration of chemotherapy-induced anemia.

Anemia is a common complication in patients with cancer.[1,2] Anemia, defined by low hemoglobin or a low red blood cell (RBC) count, can be a consequence of the myelotoxicity of the chemotherapy regimen (especially platinum-containing regimens) or an inherent effect of the cancer itself (particularly in multiple myeloma, lymphomas, or metastatic bone disease). Although approximately 50% of patients receiving chemotherapy can experience anemia of varying severity,[3] and despite the attendant morbidities—which can include fatigue and cognitive and other central nervous system effects[4,5]—anemia represents an undertreated complication in cancer patients.

Since its introduction in 1989, recombinant human erythropoietin (rHuEPO) has been a mainstay for the treatment of cancer-related anemia that reduces the need for RBC transfusions.[6] When anemic cancer patients receiving chemotherapy were treated with a standard regimen

of rHuEPO, hemoglobin response (defined as an increase in hemoglobin \geq 2 g/dL) was seen in 53% of patients.[7] Additionally, the requirement for blood transfusions was significantly decreased and quality-of-life indices were significantly improved.

Recommended dosing of rHuEPO is three times weekly, although weekly regimens are commonly utilized in cancer patients.[8] This requirement

for frequent dosing is due to the relatively short serum half-life of rHuEPO. In response to this shortcoming in dosing profile, a novel molecule was designed. Site-directed mutagenesis was employed to modify the amino acid backbone of human erythropoietin to allow for additional N-linked sialic acid-containing carbohydrate chains. These additional sialic acid moieties act to slow the clearance of

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the glycoprotein and hence prolong the serum half-life.

The resulting molecule, darbepoetin alfa (Aranesp), is a unique erythropoietic protein with a greater *in vivo* potency relative to rHuEPO.[9] This increased biologic activity is due primarily to the slower clearance of the molecule. Following intravenous administration to patients with chronic kidney disease, the terminal half-life was 25.3 hours, approximately threefold longer than that of rHuEPO.[10] In subcutaneous usage, the rate of absorption from the subcutaneous administration site controls the elimination rate. Following subcutaneous administration, the terminal half-life of darbepoetin alfa was 48.8 hours, approximately twofold longer than that for intravenous administration, with a bioavailability of 37%.

In phase II dose-finding trials, clear dose-dependent increases in hemoglobin response were seen.[11] In a placebo-controlled phase III study of 320 anemic lung cancer patients receiving platinum-containing chemotherapy, statistically significant improvements favoring darbepoetin alfa vs placebo were seen in the proportion of patients with a hematopoietic response (66% vs 24%), in patients requiring transfusions (26% vs 60%), and in the mean number of transfusions per patient (1.14 vs 2.64).[12] Darbepoetin alfa is approved in the United States and Europe for the treatment of anemia associated with chronic renal failure (including dialysis and predialysis patients) and in the United States for the treatment of chemotherapy-induced anemia in patients with non-myeloid malignancies.

Due to the longer serum half-life, darbepoetin alfa should be administered less frequently than rHuEPO.[13] This provides obvious advantages for both patients and health-care providers. The current recommendation for rHuEPO dosing in cancer patients

with chemotherapy-induced anemia is a starting dose of 150 U/kg three times weekly, adjusted in accordance with resulting hemoglobin levels.[14] Approved dosing for darbepoetin alfa in this same setting is 2.25 µg/kg once weekly.[13] However, a comparative study indicated that darbepoetin alfa administered at 1.5 µg/kg once weekly produced a similar mean hemoglobin change from baseline as the above three-times-weekly regimen of rHuEPO.[11,15]

Alternative dosing strategies for darbepoetin alfa have been tested that more fully exploit the pharmacokinetic profile. These include dosing every 2 weeks,[11] where it has been demonstrated that darbepoetin alfa at 3 µg/kg every 2 weeks produced the same hematopoietic response as rHuEPO given at 40,000 U once weekly—a typical weekly dose. Even longer dosing intervals are being explored to coincide with the cycle of chemotherapy (*viz*, every 3 weeks and every 4 weeks).[16]

An additional dosing paradigm that might serve to enhance the utility of darbepoetin alfa is a fixed dose, *ie*, a dosing regimen independent of patients' body weight. A fixed dose would contribute to the simplicity of darbepoetin alfa usage and, by the administration of the entire contents of a vial, eliminate wasted product. However, a thorough understanding of the pharmacokinetic/pharmacodynamic profile of darbepoetin alfa is necessary to ensure the success of a fixed-dose strategy. Other relevant considerations would include the distribution of body weight in the oncology population, the potential for under- or overdosing patients, and attendant benefit/risk issues.

Clinical trial simulation that includes the integration of pharmacokinetic and pharmacodynamic modeling has been advocated as a means of applying modeling techniques to drug development.[17-20] The Monte Carlo method is one such technique for performing clinical trial simulation.[21] Pharmacokinetic/pharmacodynamic modeling based on population analysis with subsequent Monte Carlo simulations would potentially provide the best and least biased

estimate of the anticipated hemoglobin response both within the treated population and for an individual with specific characteristics. This methodology permits the incorporation of measures of variability and uncertainty into pharmacokinetic/pharmacodynamic modeling.[22-26] Monte Carlo simulation uses prior information, such as baseline body weight and hemoglobin concentration, and parameter estimates (from the pharmacokinetic/pharmacodynamic model), and allows multiple sampling of these quantitatively defined probability distributions and the subsequent computation of model outputs. This method allows for a more rigorous assessment of variability of response than simpler (mean parameter or deterministic) methods.

This paper presents the results of a clinical trial simulation using the Monte Carlo method that assesses the predicted hematopoietic response of a fixed dose of darbepoetin alfa (200 µg every 2 weeks) vs modeled results for a weight-based dose (3 µg/kg every 2 weeks). Model validation was performed by comparing predicted outcomes for weight-based dosing with observed clinical data from weight-based dosing.

Methods

Source of Clinical Data

Clinical data for 547 patients were utilized in generating the model for the simulation. These patients had participated in one of three Amgen-sponsored clinical trials of darbepoetin alfa for chemotherapy-induced anemia (study numbers 980290, 980291, and 20000174).[11,16,27] These trials were similar in nature, all being conducted in a multicycle chemotherapy setting for adult patients with solid tumors. Patients were required to have a baseline hemoglobin ≤ 11 g/dL for study eligibility. The trials investigated various doses and schedules of darbepoetin alfa in a randomized sequential- or parallel-cohort structure. Doses and schedules of darbepoetin alfa that were studied included 0.5 through 18 µg/kg given every week, every 2 weeks, every 3 weeks, and every 4 weeks

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(a total of 18 different regimens) over a 12-week treatment period.

Table 1 gives descriptive statistics on the demographics of the 547 patients whose data were used in the model development. Over two-thirds of the population were female, due to the prevalence of breast and gynecologic cancer patients treated in these trials. Across the three trials, the mean age of the patients was 61 years (range: 20 to 91 years). Mean body weight was 70 kg (range: 39 to 129 kg). Tumor types represented in this population included—in descending order of prevalence—breast, lung, gastrointestinal, gynecologic, and genitourinary. Platinum-containing regimens were used in approximately 38% of patients across all three studies.

In addition to serial hemoglobin levels representing the pharmacodynamic response, serum drug levels for the pharmacokinetic response were measured intensively in five patients given darbepoetin alfa doses of 0.5, 1.5, or 4.5 $\mu\text{g/kg}$ once weekly subcutaneously, and were also measured predose and 48 hours postdose in 211 patients at certain dosing time points. Observed clinical data from 33 patients in study 980290[11] who received darbepoetin alfa in a 3.0 $\mu\text{g/kg}$ every-2-week regimen were utilized for comparison with the simulated fixed dose and the simulated weight-based dose.

Modeling and Simulation Procedures

Pharmacokinetic/pharmacodynamic modeling and clinical trial simulation were used to evaluate every-2-week dosing of darbepoetin alfa and to assess the impact of a fixed dose on predicted response and its variability. The modeling and clinical trial simulation steps were as follows: (1) fitting and optimizing the model to data from the three darbepoetin alfa clinical studies (described above), (2) developing a clinical trial simulation platform by incorporating relevant clinical study design elements, and (3) performing clinical trial simulations to evaluate the impact of a fixed dose of darbepoetin alfa on predicted response and its variability.

Darbepoetin Alfa Pharmacokinetic/Pharmacodynamic Structural Model

The basis of the pharmacokinetic/pharmacodynamic model is the relationship between darbepoetin alfa and hemoglobin concentrations, as demonstrated in dogs.[28] The erythropoiesis pharmacokinetic/pharmacodynamic structural model is an indirect response model incorporating RBC physiology (Figure 1). The model assumes that darbepoetin alfa concentrations stimulate the production rate of RBCs in the bone marrow at the precursor stage. The production rate is increased by a factor proportional to E_{max} , with half-maximal stimulation observed at a serum drug concentration of EC_{50} . The stimulation function occurs in the first of a series of compartments with equal transfer coefficients; this might be considered physiologically equivalent to the bone marrow (Figure 1).

The total maturation transit time in the "bone marrow" is considered to be similar to the RBC production time. The "bone marrow" is linked to the RBCs in circulation or "hemoglobin compartment" (a linked series of compartments that have equal transfer coefficients with elimination from the terminal compartment to allow for aging of the RBCs). The total transit time of the RBCs in circulation is representative of the RBC lifespan.

Pharmacokinetic/Pharmacodynamic Modeling

The pharmacokinetic and pharmacodynamic parameters and associated covariances for this population were estimated simultaneously using data from the three darbepoetin alfa clinical studies cited above with BigNPEM.[29] Pharmacokinetic parameter estimates were determined first from available intensive pharmacokinetic profiles, then updated using predose and 48-hour postdose data from 211 additional patients. Previous analyses demonstrated that the pharmacokinetic properties of darbepoetin alfa are dose- and time-linear.[10] The pharmacokinetic parameters were then fixed to allow estimation of the pharmacodynamic

Table 1

Patient Demographic Variables

	Patients Used in Model Development
Number of patients	547
Males	31%
Females	69%
Age	
Mean (SD)	61.4 yr (12.3 yr)
Minimum/maximum	20 yr/91 yr
Body weight	
Mean (SD)	69.8 kg (15.2 kg)
Minimum/maximum	39 kg/129 kg
Tumor type	
Breast	28%
Lung	21%
Gastrointestinal	19%
Gynecologic	17%
Genitourinary	6%
Other	9%
Patients with a platinum-containing chemotherapy regimen	38%

SD = standard deviation.

parameters. Hemoglobin response data were used from the 547 patients discussed above. Mean response data for all treatment groups were fitted simultaneously.

The mean parameter vector was optimized for the 3 $\mu\text{g/kg}$ every-2-week dosing paradigm to make model predictions of responses for this treatment regimen. A posterior predictive check on model performance was performed using both simulated patients and observed clinical trial results. The predicted-vs-observed plots following the generation of maximal a posteriori Bayesian probability estimates for each regimen showed that the pharmacokinetic/pharmacodynamic model accurately predicted the observed hemoglobin profiles across all 18 treatment regi-

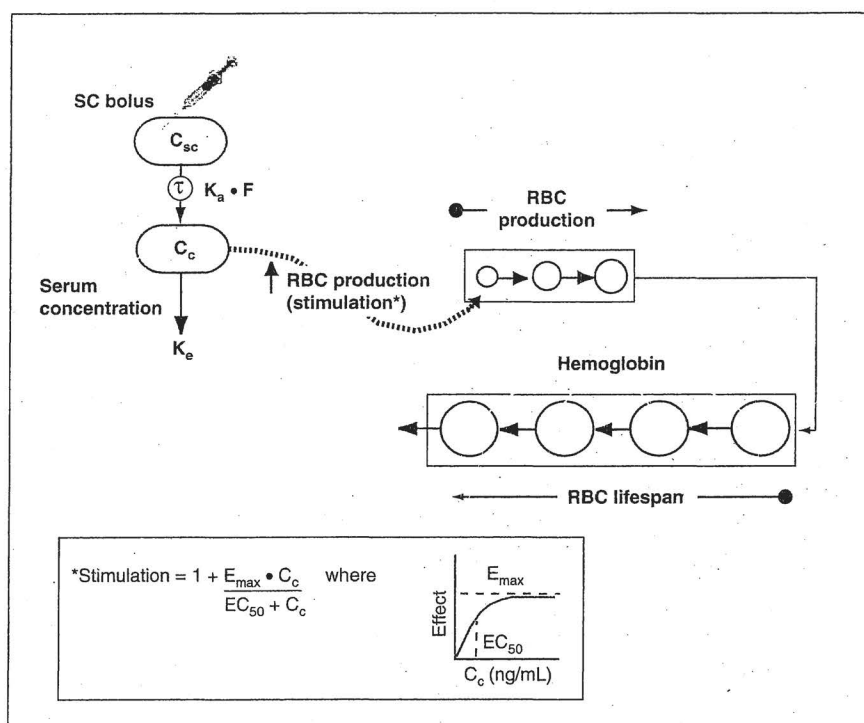


Figure 1: Erythropoiesis Pharmacokinetic/Pharmacodynamic Structural Model—An indirect response model based on the relationship between darbepoetin alfa and hemoglobin concentrations. The model involves a series of dynamically linked compartments representing changes in darbepoetin alfa serum concentrations, stimulation of RBC production, and subsequent RBC maturation and death. K_e (CL/ V_c , day⁻¹) = elimination from the central compartment; CL (mL/kg/day) = clearance; V_c (mL/kg) = volume of distribution in central compartment; K_a (day⁻¹) = first-order absorption rate; τ (days) = lag time of absorption; F = bioavailability following SC dosing; C_{sc} (ng) = drug mass at injection site; C_c (ng/mL) = drug concentration in central (serum) compartment; E_{max} (ng/mL) = maximum effect; EC_{50} (ng/mL) = serum concentration at which half-maximal effect is observed; RBC = red blood cell; SC = subcutaneous.

mens ($r^2 \geq 0.95$), demonstrating the utility of this model in describing hemoglobin response following administration of various regimens of darbepoetin alfa.

Clinical Trial Simulation

Development of the clinical trial simulation platform encompassed the following elements:

- Determination of pharmacokinetic and pharmacodynamic parameter estimates and their associated variability and distribution from a relevant population (described above)
- Definition of population baseline characteristics and the associated distribution (body weight and baseline hemoglobin from the darbepoetin alfa clinical studies were assumed to be representative of the population)

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- Implementation of a transfusion intervention mechanism: using hemoglobin ≤ 8.0 g/dL as a transfusion trigger, hemoglobin data for these patients were censored for the next 4 weeks, but the patient was not eliminated altogether from the analysis

- Allowance for darbepoetin alfa dose interruptions (dosing was withheld when hemoglobin was ≥ 14.0 g/dL for women and ≥ 15.0 g/dL for men as in the actual clinical studies)

- Censoring was randomly implemented in the simulated cohorts to coincide with the incidence of observed dropout rates in the clinical trials

- Incorporation of other elements of the protocol, eg, duration of dosing and definitions of response

Clinical trial simulation (5,000 patients/cohort) was performed in order to predict outcomes and associated variability for each of the dose cohorts (weight-based vs fixed dose of darbepoetin alfa). These simulations were performed by sampling from the distributions of each of the parameters and baseline characteristics to enable assessment of predicted outcomes. All statistics for the simulated cohorts were derived directly from the clinical trial simulations.

Results

Hemoglobin End Points

Mean hemoglobin change from baseline over time is plotted in Figure 2 for the simulation of a weight-based dose (3 μ g/kg every 2 weeks) and the simulation of a fixed dose (200 μ g every 2 weeks), vs the observed data of 33 patients who received darbepoetin alfa at 3 μ g/kg every 2 weeks. The two simulated curves are virtually superimposed, with mean hemoglobin changes from baseline increasing over time throughout the 12-week treatment period. The observed data for 3 μ g/kg every 2 weeks compared closely with the simulated data. Standard deviations were similar in magnitude across all three groups, indicative of comparable variability in the respective populations. Overall, these hemoglobin profiles demonstrated close similarity between the observed data and the simulations and provide validation for the model.

Mean changes in hemoglobin concentration between baseline and various posttreatment time points (Table 2) also illustrate the similarity between the three data sets. At day 84, mean hemoglobin change from baseline for the observed data cohort was +1.61 g/dL (standard deviation [SD] 1.7 g/dL), compared with 1.83 g/dL (SD 1.5 g/dL) for the weight-based dose simulation and +1.79 g/dL (SD 1.5 g/dL) for the fixed-dose simulation.

Additional hemoglobin end points

for the three cohorts are summarized in Table 3; these include the proportion of patients achieving a hemoglobin response (eg, an increase of ≥ 2 g/dL from baseline) and patients requiring one or more RBC transfusions. For each end point, the two simulated cohorts gave comparable results. The proportion of patients who demonstrated a hemoglobin response was 60% in the observed data, compared with 77% and 76% in the simulations; however, the 95% confidence intervals in the former overlapped the simulated values.

The RBC transfusion trigger was reached in 21% and 22% of simulated patients in the weight-based and fixed-dose cohorts, respectively. These rates were higher than the rate of actual transfusion usage in the observed data (16%), possibly due to the subjectivity of clinicians in choosing to transfuse real patients, whereas in the simulation a "transfusion" was automatic at a hemoglobin concentration ≤ 8 g/dL. However, the simulated transfusion rates were lower than the rate of 26% reported from patients receiving darbepoetin alfa at 2.25 μ g/kg once weekly in the phase III placebo-controlled trial.[12]

Effects of Body Weight

Figure 3 provides a profile of body weight distribution using 1,180 patients who received darbepoetin alfa, rHuEPO, or placebo across four oncology trials. Mean and median body weights were 70 and 69 kg, respectively, with a range of 35 to 165 kg. Fifty percent of the patients in this population fell within body weights of 59 and 79 kg, and 90% were between 48 and 96 kg.

Figure 4 shows mean change in hemoglobin concentration from baseline to day 84 (end of treatment period) by body weight class for the two simulated dosing groups and for the observed group. As might be predicted, the profile for the weight-based dosing simulation showed little variation in hemoglobin by body weight class, with mean hemoglobin changes between +1.7 and +1.9 g/dL across all weight classes. The fixed-dose simulation showed some weight effect trend as expected, with a higher

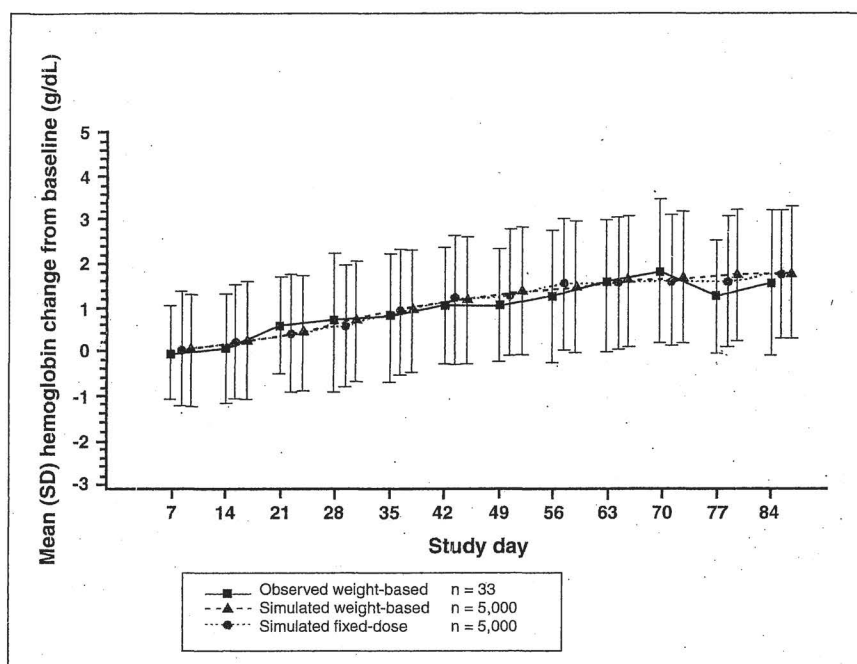


Figure 2: Hemoglobin Change From Baseline Over Time—Mean and standard deviation of hemoglobin change from baseline for observed data, simulated weight-based data, and simulated fixed-dose data. Hemoglobin values within 28 days after a red blood cell transfusion were excluded (or at a hemoglobin value of ≤ 8 g/dL for simulated data). SD = standard deviation.

Table 2

Mean Hemoglobin Change From Baseline

	Observed Data (3 μ g/kg q2wk)	Simulated Weight- Based Dose (3 μ g/kg q2wk)	Simulated Fixed Dose (200 μ g q2wk)
Hemoglobin change from baseline to day 28			
Number of patients	25	3,886	3,835
Mean (SD)	0.72 g/dL (1.6 g/dL)	0.72 g/dL (1.4 g/dL)	0.63 g/dL (1.4 g/dL)
Hemoglobin change from baseline to day 56			
Number of patients	23	4,092	3,985
Mean (SD)	1.29 g/dL (1.5 g/dL)	1.51 g/dL (1.5 g/dL)	1.56 g/dL (1.5 g/dL)
Hemoglobin change from baseline to day 84			
Number of patients	15	3,812	3,812
Mean (SD)	1.61 g/dL (1.7 g/dL)	1.83 g/dL (1.5 g/dL)	1.79 g/dL (1.5 g/dL)

q2wk = every 2 weeks; SD = standard deviation.

mean hemoglobin change from baseline at the lowest (< 45 kg) body weight class (+2.11 g/dL [SD 1.55 g/dL]), slight decreases with increasing body weight, and the lowest change in he-

moglobin at the highest (> 95 kg) body weight class (+1.15 g/dL [SD 1.46 g/dL]). Importantly, however, at the central portion of the weight distribution (ie, between 45 and 95 kg

Table 3

Comparison of Hemoglobin Response Variables

	Observed Data (3 µg/kg q2wk)	Simulated Weight- Based Dose (3 µg/kg q2wk)	Simulated Fixed Dose (200 µg q2wk)
Number of patients	33	5,000	5,000
Patients with hemoglobin increase ≥ 2 g/dL ^a	60% (39%–80%)	77% (76%–79%)	76% (75%–77%)
Patients with RBC transfusion ^{a,b}	16% (3%–29%)	21% (20%–23%)	22% (21%–23%)

^aKaplan-Meier proportion (95% confidence interval).^bTransfusions were given (or simulated) when hemoglobin concentration was ≤ 8 g/dL.

q2wk = every 2 weeks; RBC = red blood cell.

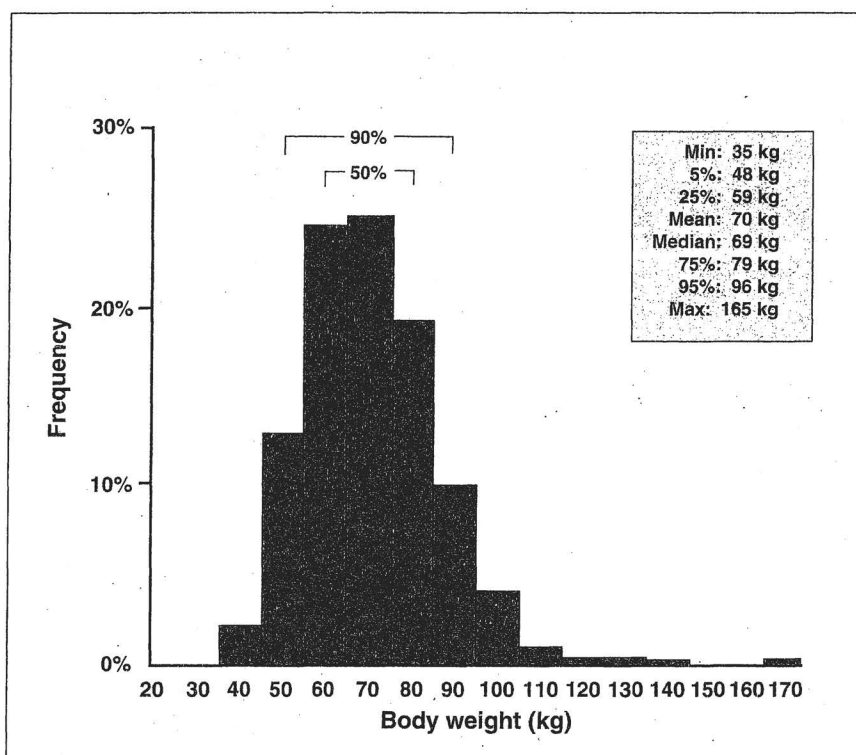


Figure 3: Body Weight Distribution Across Darbepoetin Alfa Clinical Trials—Frequency of body weight values for 1,180 cancer patients participating in darbepoetin alfa trials, showing 50th and 90th percentiles.

body weight, representing over 90% of the population), the weight-based dose and the fixed-dose simulations were within 0.2 g/dL of each other in terms of hemoglobin change from baseline.

Comparing the weight distribution in Figure 3 with the hemoglobin re-

sponses by weight class in Figure 4, it is clear that the majority of patients would be expected to benefit equally from a weight-based and a fixed dose of darbepoetin alfa.

Table 4 illustrates the weight-based dose equivalent of a 200-µg fixed dose of darbepoetin alfa for

body weights from 40 to 100 kg. Dosing a 40-kg patient with 200 µg of darbepoetin alfa equates to 5.0 µg/kg; for a 100-kg patient, the weight-based equivalent is 2.0 µg/kg. These doses have been studied in clinical trials and have been shown to be safe and to have biologic activity.[11] In practice, some patients will require titration of their dose of darbepoetin alfa in order to achieve optimal hematopoietic response. In general, however, the model predicts that a fixed darbepoetin alfa dose of 200 µg every 2 weeks and a weight-based dose of 3 µg/kg every 2 weeks would provide similar efficacy for the majority of cancer patients with chemotherapy-induced anemia.

Summary and Discussion

Previous work has demonstrated that darbepoetin alfa administered at 3 µg/kg every 2 weeks was as efficacious as a standard regimen of rHuEPO in eliciting hemoglobin increases in cancer patients with chemotherapy-induced anemia.[11] The Monte Carlo clinical trial simulation presented in this paper demonstrated the comparability between these observed clinical data from weight-based dosing of darbepoetin alfa and a simulation of weight-based dosing. Additionally, simulated hematopoietic outcomes from a fixed dose of darbepoetin alfa were comparable with those from both simulated and actual weight-based dosing.

In considering the feasibility and utility of a fixed dose for darbepoetin alfa (eg, a regimen independent of a patient's body weight) for the treatment of cancer patients with chemotherapy-induced anemia, the following questions must be addressed:

- In terms of net benefit, are the needs of the vast majority of the population amply addressed?
- For patients at the upper end of the body weight distribution, is there risk of underdosing and thus compromising efficacy?
- For patients at the lower end of the body weight distribution, is there risk of overdosing and possibly encountering safety issues?

Simulated hematopoietic response

to darbepoetin alfa by patient weight class indicated only a slight weight effect with a fixed-dose regimen in terms of change in hemoglobin from baseline. Importantly, given the data on weight distribution from a typical oncology patient population, the majority of patients would be appropriately initiated on treatment with a fixed darbepoetin alfa dose of 200 μ g every 2 weeks. Regardless of the use of weight-based or fixed dosing for erythropoietic agents, due to the multiple variables that cause anemia and influence erythropoiesis in these patients, standard practice requires dose titration to the desired hemoglobin concentration.

The minor role that body weight plays in determining hematopoietic response for any given individual is not unexpected given the overall complexity of the disease state. On a population level, responsiveness to erythropoietic factors (quantified by the EC_{50}) appears to be determined primarily by disease state. For example, patients with chronic kidney disease are generally more responsive to erythropoietic factors than are cancer patients with underlying anemia, who in turn are more responsive than cancer patients with chemotherapy-induced anemia; this phenomenon is manifested in varying dose requirements for these agents. Chronic kidney disease is characterized by a deficiency in endogenous erythropoietin that requires simple replacement therapy, whereas cancer patients receiving chemotherapy have compromised bone marrow that interferes with their ability to respond normally to erythropoietic agents.

Other potential factors include baseline hemoglobin and endogenous erythropoietin concentrations, concurrent medications, and nutritional factors. The lower the EC_{50} of an agent, the more responsive the patient. Sensitivity analyses have verified that the variability in EC_{50} of darbepoetin alfa (ranging from 0.062 to 9.023 ng/mL) is far more important with regard to pharmacodynamic effect than are body weight differences in the population.

Safety issues, of theoretical concern with a fixed dose at lower body

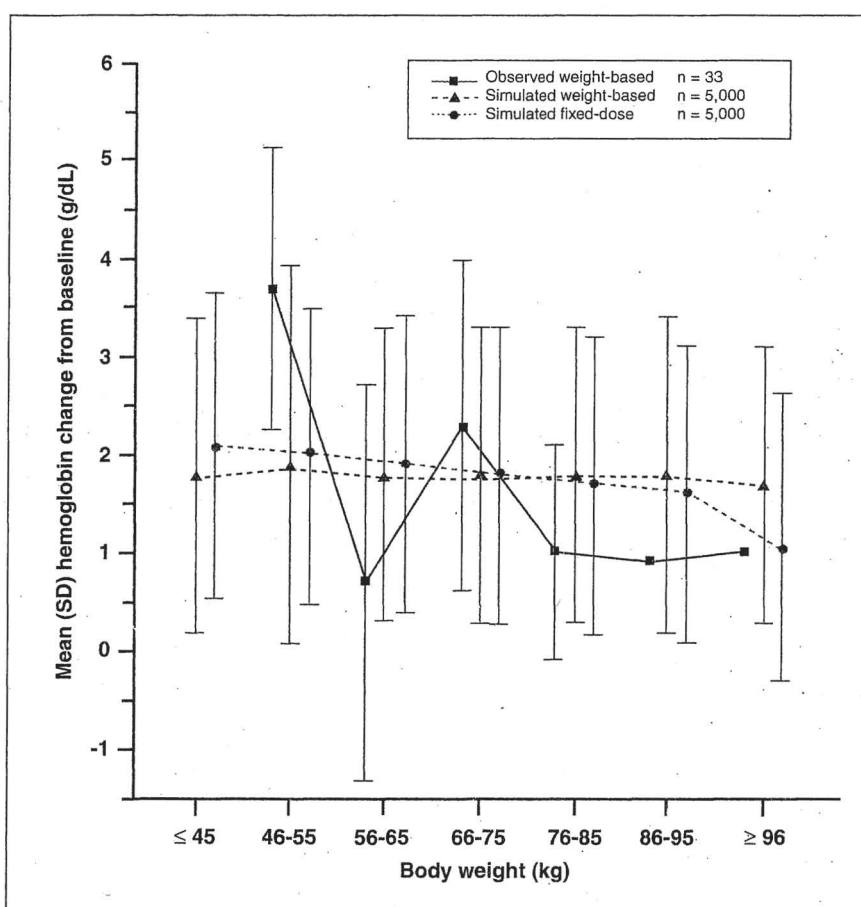


Figure 4: Hemoglobin Change From Baseline by Body Weight Class— Mean and standard deviation of change in hemoglobin concentration between baseline and end of treatment (day 84) for observed clinical data, simulated weight-based data, and simulated fixed-dose data by body weight class.

Table 4

Dosing Chart of 200- μ g Darbepoetin Alfa by Body Weight

Body Weight	Fixed Darbepoetin Alfa Dose	Equivalent Weight-Based Dose
40 kg	200 μ g	5.00 μ g/kg
50 kg	200 μ g	4.00 μ g/kg
60 kg	200 μ g	3.33 μ g/kg
70 kg	200 μ g	2.86 μ g/kg
80 kg	200 μ g	2.50 μ g/kg
90 kg	200 μ g	2.22 μ g/kg
100 kg	200 μ g	2.00 μ g/kg

weight extremes, are minimal with darbepoetin alfa. Commonly reported adverse events in cancer patients receiving darbepoetin alfa were consistent with those in anemic patients receiving cytotoxic chemotherapy, and included fatigue, edema, nausea, vomiting, diarrhea, fever, and dyspnea.[13]

In terms of overall cost efficiency of a fixed dose for darbepoetin alfa, the weight distribution of a typical cancer population indicates that most patients would receive a dose similar to the 3 µg/kg every-2-week target, and those who would receive more drug at a fixed dose of 200 µg every 2 weeks vs the weight-based dose are approximately balanced by those who would receive less. Importantly, by using the entire contents of a 200-µg vial, no drug would be discarded; furthermore, labor costs associated with measuring an exact weight-based dose of drug would be eliminated.

In summary, the clinical trial simulation presented in this paper indicated that a fixed 200-µg dose of darbepoetin alfa administered every 2 weeks would be as effective as a weight-based dose of 3 µg/kg every 2 weeks in ameliorating anemia in patients with solid tumors who are receiving chemotherapy. A definitive demonstration of this inference would require a prospective clinical trial. There are minimal safety concerns for patients at a lower body weight extreme based on cumulative clinical experience with darbepoetin alfa. For patients who display an inadequate (or excessive) hematopoietic response to this starting fixed-dose regimen, standard practice calls for titration of dose according to resulting hemoglobin concentrations.

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